

Claims:

1. The use of a compound, which is a serotonin reuptake inhibitor, and a compound, which is a GlyT-1 inhibitor for the preparation of a pharmaceutical composition for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.
2. The use of a GlyT-1 inhibitor for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor.
3. The use of a GlyT-1 inhibitor for the preparation of a pharmaceutical composition useful for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor.
4. The use according to any of claims 2-3 wherein the serotonin reuptake inhibitor is used for the treatment of depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to a SRI.
5. The use according to any one of claims 1-4 wherein the SRI is selected from a SSRI.
6. The use according to any one of claims 1-5 wherein the SRI is elected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine,

dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine.

7. The use according to any one of claims 1-6 wherein the GlyT-1 inhibitor is
5 selected from
N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl} glycine
ethyl ester,
N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylglycine ethyl ester,
10 N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl} glycine,
N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylglycine,
N-{3-[1-(3-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylglycine,
15 N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylglycine,
N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methyl (1-ethyl)glycine,
N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
20 methylglycine,
N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylglycine,
N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylalanine,
25 N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-
ethyl)glycine,
N-{3-[4-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-
propyl}-N-methylglycine,
N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
30 methylglycine,
N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-
methylalanine,

- N-{3-[6-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
5 N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[6-chloro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[5-fluoro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
10 N-{3-[5-fluoro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
15 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,
N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[5-cyano-1-(4-cyanophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,
20 N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
N-{3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine, N-{2-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]ethyl}-N-methylglycine,
25 N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine,
N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine,
N-{3-[3-cyclo-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
30 N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylglycine,
N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine,

- N-{3-[1-(4-Fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methylglycine,
- N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,
- 5 N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine,
- N-[3-(3-methyl-1-phenyl-1*H*-inden-1-yl)-propyl]-N-methylglycine,
- N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,
- 10 N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,
- N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,
- 15 N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,
- N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,
- N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,
- 20 N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,
- N-[3-(3,3-Diethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- 25 N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,
- N-[3-(1-phenyl-1,3-dihydro-benzo[*c*]thiophen-1-yl)-propyl]-N-methylalanine,
- 30 N-{3-[1-(4-Chloro-phenyl)-3,3-dimethyl-indan-1-yl]-propyl}-N-methylglycine,
- N-{3-[1-(4-Chloro-phenyl)-3,3-diethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-alanine,
- N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine,

- N-[3-(1-phenyl-(1*H*)-inden-1-yl)-propyl]-N-methyl-alanine,
N-{3-[1-(4-Fluoro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methyl-glycine,
5 N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methyl-alanine,
N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
10 N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
15 N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
20 N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{2-[1-(4-Chloro-phenyl)-5-(5-chloro-thiophen-2-yl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
25 N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
30 N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,

- N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,
 N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
 5 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
 N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
 N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
 10 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,
 N-{3-[1-(4-chloro-phenyl)-5-(2-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,
 15 (+/-)-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
 (+/-)-{4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
 (+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
 20 (+/-)-{4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
 (+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid,
 25 (+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid,
 (+/-)-2-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethylpiperazin-1-yl}-propionic acid,
 {4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid,
 30 {4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2(R),5(S)-dimethyl-piperazin-1-yl}-acetic acid,

- {4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2,2-dimethyl-piperazin-1-yl}-acetic acid,
(+/-)-{4-[5-Chloro-2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid,
5 {4-[5-Chloro-2-(3-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid,
(+/-)-{4-[2-(4-Phenyl-phenyloxy)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid,
(+/-)-{4-[2-(4-Methyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
10 (+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
(+/-)-{4-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid,
(+/-)-2-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-3-methylpiperazin-1-yl}-
15 propionic acid,
{4-[2-(4-Isopropyl-phenylsulfanyl)-phenyl]-piperazin-1-yl}-acetic acid,
(+/-)-2-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-3-methyl-piperazin-1-yl}-propionic acid,
or a pharmaceutically acceptable acid addition salt thereof.
20
8. A pharmaceutical composition comprising a compound, which is a serotonin reuptake inhibitor, and a compound, which is a GlyT-1 inhibitor, and optionally pharmaceutically acceptable carriers or diluents.
- 25 9. The pharmaceutical composition of claim 8 wherein the SRI is selected from a SSRI.
10. The pharmaceutical composition of claim 8 or 9 wherein the GlyT-1 inhibitor show inhibition below 20000 nM, such as below 10000 nM, as IC₅₀ in the "[³H]-
30 Glycine uptake" test described herein.
11. The pharmaceutical composition of any one of claims 8-10 wherein the GlyT-1 inhibitor is selected from any one of the inhibitors of claim 7.

12. The pharmaceutical composition according to any one of claims 8-11 characterized in that the serotonin uptake inhibitor is selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine.
- 5 13. The pharmaceutical composition according to any one of claims 8-12, which is adapted for simultaneous administration of the active ingredients.
- 10 14. The pharmaceutical composition according to claim 13 wherein the active ingredients are contained in the same unit dosage form.
- 15 15. The pharmaceutical composition according to any one of claims 8-12 which is adapted for sequential administration of the active ingredients.
16. The pharmaceutical composition according to any one of claims 13 and 15 wherein the active ingredients are contained in discrete dosage forms.
- 20 17. A kit comprising a compound, which is a serotonin reuptake inhibitor, and a compound, which is a GlyT-1 inhibitor, and optionally pharmaceutically acceptable carriers or diluents.
- 25 18. A method for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors comprising administering to a person in need thereof a therapeutically effective amount of a compound, which is a serotonin reuptake inhibitor and a compound, which is a GlyT-1 inhibitor.
- 30